PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X15711	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/03349	International filing date *(day/month/year)* 16.07.2003	Priority date *(day/month/year)* 22.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/4453		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.12.2003	20.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Johnson, C Telephone No. +49 89 2399-8287

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/03349

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-106 as originally filed

Claims, Numbers

1-22 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 15,16

   because:

   ☒ the said international application, or the said claims Nos. 15,16 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	6-13,21,22
	No:	Claims	1-5, 14-20
Industrial applicability (IA)	Yes:	Claims	1-14,17-22
	No:	Claims	

2. Citations and explanations

   see separate sheet

III. Non-establishment of opinion

Claims 15 and 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V. Reasoned statement

Reference is made to the following documents:
D1: EP-A 791 591
D2: Grese et al., J. Med. Chem. 1997, 40, 146-167

Novelty

The compounds of claim 1 differ from those of D1 because the nitrogen atom of the N-containing heterocyclic ring is not oxidized and from those of D2 because of the $-SO_2R^1$ substituent. The compounds of claim 18 differ from those of D1 because they are not N-oxides and from those of D2 because of the proviso.

Claims 1-22 fulfil the requirements of Article 33(2) PCT.

Inventive step

The technical problem underlying the present application appears to be the provision of selective estrogen receptor modulators and their intermediates. D1 and D2 relate to compounds with affinity for the estrogen receptor. Example 1 of D1 differs from raloxifene, compound 1 of D2, only in that the N-atom is oxidized. Both compounds have affinity for the estrogen receptor. A combination of these documents therefore teaches the skilled man that analogues of D1 in which the N-atom is not oxidized may be expected to have qualitatively the same activity as the N-oxides. It would thus be obvious for the skilled man, seeking to provide further compounds with the same activity, to modify the compounds of D1 by removing the N-oxide group and hence to arrive at compounds falling within claims 1-5 and 14 and to use them as claimed in claims 15-17.

Insofar as the compounds of claim 18 have an affinity for the estrogen receptor, they are considered obvious for the same reasons as those given for claim 1 (both D1 and D2 also disclose compounds wherein the benzothiophene group is e.g. 6-alkoxylated, hence the removal of the N-oxide of such compounds would be expected to lead to compounds with the desired activity). Insofar as the compounds of claim 18 are intermediates for preparing the compounds of claim 1,

it is mentioned in D1 that protected hydroxy derivatives may be used to prepare the desired final product (p. 5, l. 52-54). It would thus be obvious to use e.g. benzyloxy compounds of claim 18 to prepare the hydroxy final product of claim 1. Claims 18-20 are therefore obvious.

It is noted that there is a discrepancy between the abstract and claim 1 of D1, in which R^1 may be $-SO_2$alkyl, and the summary of the invention on p. 4, in which R^1 may be $-OSO_2$alkyl but not SO_2alkyl. A further part of D1 refers to sulfonates of formula II which may be converted to the N-oxides of formula I. However, this discrepancy does not result in the negation of the teaching in claim 1 of D1 that compounds of formula (I) in which $R^2 = R^1 = -SO_2$alkyl display affinity for the estrogen receptor. Even if the skilled man did notice the discrepancy, he would not know with any degree of certainty which definition of R^1 is in error or whether indeed both were intended. Under Rule 91 PCT, obvious errors in an international application may be rectified when anyone would immediately realise that nothing else could have been intended than what is offered as rectification. The same criteria should be used in interpreting the prior art. As it is not clear that in D1 nothing else could have been intended other than the definition of R^1 as OSO_2alkyl, this document must be interpreted in its broadest form, i.e. as including both possibilities for R^1.

Claims 1-5, 14-20 do not fulfil the requirements of Article 33(3) PCT.

As D1 and D2 both concern benzothiophene derivatives, and no documents have been found suggesting the functional equivalence of naphthyl and benzothiophene rings in similar compounds with estrogen receptor modulation activity, the naphthyl compounds of claims 6-13, 21 and 22 are considered to be inventive, insofar as they have the alleged activity.

Claims 6-13, 21 and 22 fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 1-14, 17-22 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claims 15 and 16 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical

treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.